

Genetic and clinical determinants of abdominal aortic diameter: Genome-wide association studies, exome array data and Mendelian randomization study

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Abstract

Progressive dilation of the infrarenal aortic diameter is a consequence of the ageing process and is considered the main determinant of Abdominal Aortic Aneurysm (AAA).

We aimed to investigate the genetic and clinical determinants of abdominal aortic diameter (AAD). We conducted a meta-analysis of genome-wide association studies in ten cohorts (n=13,542) imputed to the 1000 Genome Project reference panel including 12,815 subjects in the discovery phase and 727 subjects (PBIO) as replication.

Maximum anterior-posterior diameter of the infrarenal aorta was used as AAD. We also included exome array data (n=14,480) from seven epidemiologic studies. Single-variant and gene-based associations were done using SeqMeta package. A Mendelian randomization analysis was applied to investigate the causal effect of a number of clinical risk factors on AAD. In GWAS on AAD, rs74448815 in the intronic region of *LDLRAD4* reached genome-wide significance (beta=-0.02, SE=0.004, p-value= 2.10×10^{-8}). The association replicated in the PBIO1 cohort (p-value= 8.19×10^{-4}). In exome-array single-variant analysis (p-value threshold= 9×10^{-7}), the lowest p-value was found for rs239259 located in *SLC22A20* (beta = 0.007, p-value = 1.2×10^{-5}). In the gene-based analysis (p-value threshold= 1.85×10^{-6}), *PCSK5* showed an association with AAD (p-value= 8.03×10^{-7}). Furthermore, in Mendelian randomization analyses, we found evidence for genetic association of pulse pressure (beta=-0.003, p-value=0.02), triglycerides (beta=-0.16, p-value=0.008) and height (beta= 0.03, p-value<0.0001), known risk factors for AAA, consistent with a causal association with AAD. Our findings point to new biology as well as highlighting gene regions in mechanisms that have previously been implicated in the genetics of other vascular diseases.

Introduction

Abdominal aortic diameter (AAD) is an index to measure the widening of abdominal aorta and therefore is a parameter for screening, surveillance and clinical management of abdominal aortic aneurysm (AAA), a focal dilatation of the abdominal aorta (1). An AAD equal or higher than 30 mm is used for diagnosis of AAA and an AAD \geq 50-55 mm is an indication for surgical intervention, depending on the patient's risk factors (2, 3). Due to the risk of rupture, AAA is potentially lethal (4) and between 1990 and 2010 the global AAA death rate has increased from 2.49 per 100,000 to 2.78 per 100,000 inhabitants (5). Progressive dilation of the aortic wall is positively associated with ageing, a higher collagen-to-elastin ratio, increased vascular stiffness and high pulse pressure (6).

Genetic and environmental factors are thought to play an important role on AAD enlargement. Evidence has shown that the variation in the diameter of healthy abdominal aorta is strongly determined by genetic factors with a heritability of 34% (7). Likewise, AAA has been shown to be more than 70% heritable (8) and individuals with a first-degree relative with AAA have a 2-fold higher risk of developing an AAA (9). Initial genetic studies conducted in populations with AAA have identified genes related to abnormal aortic dilatation. These studies have encouraged the implementation of alternative approaches to further deepen investigation of the genetics underlying aortic dilation, including the use of aortic diameter as a continuous trait, leveraging additional power over discrete trait approaches for the limited sample sizes available (10). Here, we aimed to identify genetic factors that affect AAD which was measured in the general population and within a normal range. We applied GWAS to identify (common variants) associated with AAD using data from ten studies comprising 13,542 participants and exome array analysis to identify (rare variants), using data from seven

studies on 14,480 European participants. Further, we implemented Mendelian randomization (MR) analysis to investigate the causal effect of a number of risk factors on AAD.

Results

Study sample characteristics

Baseline characteristics for each cohort included in this meta-analysis of genome-wide association studies are summarized in **Supplementary Table S1a and S1b**. The discovery panel of genome-wide analysis for common variants included 12,815 participants from nine cohorts. Mean age ranged from 45.1 to 74.9 years and the percentage of males ranged from 27.0 to 57.9. Replication of the GWAS findings was conducted in a sample of 727 individuals from P BIO1 cohort. The baseline characteristics of the samples included in the meta-analysis of exome array data are shown in **Supplementary Table S2**. We analyzed exome array data from 14,480 subjects from seven European cohorts whose mean age ranged from 49.4 to 75.3 years old and the percentage of male population ranged from 42.3 to 58.5.

Meta-analysis of genome-wide association studies

Fixed-effect meta-analysis of the summary statistics from each set identified one locus associated with AAD. **Figure 1** presents the Manhattan plot of GWAS on AAD. Genome-wide significant and suggestive SNPs ($5 \times 10^{-8} < p\text{-value} < 5 \times 10^{-7}$) are presented in **Table 1**. Quantile-quantile plots showed no genomic inflation ($\lambda=1.04$) (**Figure 2**).

The strongest association was found for rs74448815, located in the intronic region (chr18:13,593,315) of *LDLRAD4* (Low Density Lipoprotein Receptor Class A Domain Containing 4) (**Figure 3a**), where the C allele (MAF [minor allele frequency]=0.04) was associated with a smaller AAD (beta= -0.026, p-value= 2.10×10^{-7}).

⁸). This SNP was replicated in P BIO1 cohort ($p\text{-value}=8.19\times 10^{-4}$). In addition, the combined meta-analysis showed that the top hit remained genome-wide significant ($p\text{-value}=9.2\times 10^{-10}$) (**Supplementary Figure S1**) (**Table 1**).

Furthermore, we found suggestive associations ($5\times 10^{-8} < p\text{-value} < 5\times 10^{-7}$) for 12 highly correlated SNPs (genetic correlation > 0.80) located in *PLCE1* (Phospholipase C Epsilon 1) (chr10: 95,892,659-95,900,004) (**Figure 3b**) gene and 6 SNPs located in the intergenic region of *ADAMTS15* and *C11orf44* genes (**Table 1**). In a whole exome sequencing (WES) studies, *ADAMTS15* was found to be linked to intracranial aneurysm in a Japanese and German families (11, 12). *PLCE1* has been identified as a locus associated with hypertension (13), descending thoracic aneurysm (14), and with stroke in the dbGAP Gene-Trait Associations dataset (http://amp.pharm.mssm.edu/Harmonizome/gene_set/Stroke/dbGAP+Gene-Trait+Associations). Although, these variants were not successfully replicated in our analysis, we cannot exclude any indirect effect through risk factors that affect AAD. We further examined the association of AAA-risk loci, previously reported by GWAS and candidate-gene based studies (10, 15-21), with AAD (**Table 2**). *CDKN2BAS1/ANRIL* showed the strongest association with AAD (rs10757274; beta= 0.0058, $p\text{-value}=1.71\times 10^{-4}$) (19), *ERG* (rs2836411; beta=0.0034, $p\text{-value}=0.036$) (10) and *ADAMTS8* (rs4936098; beta= -0.003, $p\text{-value}=0.03$) (21) were associated with AAD at nominal significance level (**Table 2**).

We performed gene-based association analyses using MAGMA to identify tissues and pathways relevant to AAD. Input SNPs were mapped to 18,889 protein coding genes establishing a genome wide significance $p\text{-value} = 0.05/18,884 = 2.6\times 10^{-6}$.

⁶. There were no genes associated with AAD at genome-wide significance (**Supplementary Table S4**). The lowest $p\text{-value}$ was found for a set of 277 SNPs

located in *NUAK1* (NUAK Family Kinase 1) ($p\text{-value}=4.4\times 10^{-6}$). Likewise, gene set analysis revealed no significant pathways. Chondrocyte_differentiation, composed of a set of 59 genes, showed the lowest $p\text{-value}=8.1\times 10^{-5}$ (**Supplementary Table S5**).

SNP Heritability and genetic correlation

Our study included data from 13,542 participants from European ancestry. The 1KG intercept was 1.02 (standard error= 0.006). The LD-score calculated SNP Heritability showed an estimate of 0.2 and the mean χ^2 was 1.07. In addition, a cross-trait LD Score regression method was used to evaluate genome-wide genetic correlation between AAD, AAA, coronary artery disease (CAD) and stroke. We observed a positive significant correlation between AAD and AAA (genetic correlation: 0.45; $p\text{-value}=0.001$), the correlation coefficient between AAD and stroke was 0.1 ($p\text{-value}=0.3$), and between AAD and CAD was 0.06 ($p\text{-value}=0.4$).

Association of the identified SNPs with gene expression

We found that *LDLRAD4* is highly expressed in several tissues, mainly brain as well as aorta, coronary artery and tibial artery (**Supplementary Figure S2**). The isoform ENST00000359446.5, also known as hsa-miR-769-3p, reported the highest expression in arterial tissue (TPM=6.81) in comparison with other isoforms of the gene. Nevertheless, rs74448815 is an intronic SNP without a predicted function and without any proxy SNPs in coding or regulatory regions. Therefore, the effect of this SNP on miRNA regulation is yet to be explored. Likewise, we did not find expression quantitative trait loci associated with this top SNP in both *cis/trans*.

Meta-analysis of exome array data

The meta-analysis of rare exonic variants associated with AAD was conducted in 14,480 participants from seven European cohorts (**Table S2**). Meta-analysis at the single variant level of exome array variants with $\text{MAF} > 0.005$ (number of

variants=55,461) showed no significant associations with AAD. There was no evidence of genomic inflation ($\alpha=0.57$, **Supplementary Figure S3**). The lowest p-value was observed for rs239259 located in *SLC22A20* (Solute Carrier Family 22 Member 20), chromosomal region 11q13.1, where the T allele has a small effect on aortic dilation (beta=0.007, p-value= 1.20×10^{-5}). Furthermore, gene-based meta-analysis revealed an association with *PCSK5* (Proprotein Convertase Subtilisin/Kexin Type 5) (p-value= 8.03×10^{-7}), composed by 18 variants. Four variants in the *LDLRAD4* gene were identified for gene-based analysis, however, no association with AAD was observed (p-value=0.21).

Associations with cardiovascular traits

We further investigated the potential association between one genome-wide significant SNP and five suggestive SNPs found in our meta-analysis, as well as the variant with the lowest p-value reported from single variant analysis, with CAD (22) and AAA (21). We found association between our top hit, rs74448815, with a p-value=0.005 reported for CAD (**Table 3**). In contrast, our top hit was not associated with AAA (p-value=0.95) (**Table 3**). In addition, two of the suggestive SNPs located in *PLCE1* gene, rs932764 and rs2797983, showed the smallest p-value for systolic and diastolic blood pressure (23), and AAA, respectively (**Table 3**).

Genetic risk score and Mendelian Randomization analysis

We tested the association between the polygenic risk score, constructed from AAA-related SNPs, and AAD in Rotterdam Study. We found no association between the genetic score and AAD (beta=0.0004, p-value=0.09).

We further examined the potential causal association between AAA risk factors and AAD, including SBP, DBP, PP, smoking, lipid traits (LDL, HDL and TG), height and BMI. We examined 104 SNPs reported for SBP (**Supplementary Table S6**), 139

SNPs associated with DBP (**Supplementary Table S7**), 109 SNPs reported for pulse pressure (**Supplementary Table S8**), 124 variants associated with smoking (**Supplementary Table S9**), 66 SNPs for LDL (**Supplementary Table S10**), 39 SNPs for HDL (**Supplementary Table S11**), 35 SNPs for triglycerides (**Supplementary Table S12**), 134 SNPs associated with height (**Supplementary Table S13**) and 73 SNPs found for BMI (**Supplementary Table S14**).

Results from the conventional and sensitivity MR analyses are shown in Table 4. Penalized IVW estimates suggested that a 1-SD genetically-elevated height is associated with AAD (IVW estimate=0.03, p-value<0.0001) (**Supplementary Figure S3**). Furthermore, we found evidence to support that 1-SD genetically-increased pulse pressure demonstrated a significant association with infrarenal aortic diameter (IVW estimate=-0.003, p-value=0.02) (**Supplementary Figure S4**). For lipid traits, we conducted a conventional 2-sample MR analysis to assess for evidence of a causal role of LDL-cholesterol on AAD. IVW estimates were not significant for any of the each lipid fractions [LDL: IVW=-0.005, p-value=0.2 (**Supplementary Figure S5**); HDL: IVW=-0.002, p-value=0.9 (**Supplementary Figure S6**); TG: IVW=-0.02, p-value=0.2). Nevertheless, MR-Egger estimate showed that a 1-SD genetically-increase in triglycerides was significantly associated with a smaller AAD (beta=-0.16, p-value=0.008, **Supplementary Figure S7**). We did not find evidence for causal association of systolic blood pressure (IVW estimate=0.0001, p-value for IVW=0.8, **Supplementary Figure S8**), diastolic blood pressure (IVW estimate=0.001, p-value for IVW=0.5, **Supplementary Figure S9**), smoking (IVW estimate=0.02, p-value for IVW=0.3, **Supplementary Figure S10**) and body mass index (IVW estimate=-0.005, p-value for IVW=0.1, **Supplementary Figure S11**) with AAD (Table 4).

Discussion

The present study is the largest genome-wide study including both common and rare variants with AAD to date, utilizing GWAS data of 13,542 European ancestry participants from ten studies and exome array data from seven studies with 14,480 subjects. We identified two novel loci at *LDLRAD4* and *PCSK5* associated with AAD. At least one out of the 18 risk loci that were previously reported for AAA was also nominally associated with AAD. Furthermore, we showed that height and pulse pressure, known clinical risk factors for AAA, may be causally associated with AAD.

Our GWAS identified *LDLRAD4* to be associated with AAD. Prior studies have demonstrated an association of genetic variants in *LDLRAD4* with schizophrenia bipolar disorder (24, 25), and a low frequency variant (rs8096897) in this gene showed evidence of association with systolic blood pressure (26). This gene has also been described as a prognostic indicator in primary gastrointestinal stromal tumors (27). *LDLRAD4*, also known as *C18orf1*, is involved in the down regulation of transforming growth factor- β (TGF- β) by interacting with downstream effectors SMAD2 and SMAD3 via its SIM domain (28). In the canonical TGF- β pathway, ZFYVE9/SARA recruits the intracellular signal transducer and transcriptional modulators SMAD2 and SMAD3 to the TGF- β receptor. After phosphorylation by the receptor, SMAD2 and SMAD3 then form a heteromeric complex with SMAD4 that translocates to the nucleus to regulate transcription. Through interaction with SMAD2 and SMAD3, *LDLRAD4* may compete with ZFYVE9 and SMAD4 and prevent propagation of the intracellular signal.

TGF- β plays a crucial role during embryogenesis and its downregulation in adult life contributes to the development of vascular disorders, including abdominal aortic aneurysm (29). Heterozygous mutations in the genes encoding TGF- β receptors 1 and 2

(TGFBR1 and TGFBR2, respectively) cause Loeys-Dietz syndrome, an autosomal dominant aortic aneurysm syndrome, which predisposes patients to aggressive vascular disease with widespread systemic involvement (30). SMAD3 mutations play an important role in familial aortic diseases, characterized by aneurysms(31). Thus, *LDLRAD4* variants might affect AAD through the TGF- β – SMAD3 signaling axis in the general population.

The genetic basis of aortic dilation was initially explored through candidate gene approaches. Candidate genes were selected based on their biological relevance and their potential role in the pathogenesis of AAA. So far, genetic variants in eleven genes including *SORT1*, *IL6R*, *LPA*, *AGTR1*, *TGFBR2*, *ACE*, *MMP3*, *MMP13*, *MTHFD1*, *MTRR* and *LRP5* mainly implicated in lipid metabolism, inflammation, blood pressure homeostasis, TGF- β signaling, degradation of extracellular matrix and methionine metabolism, have been subject of evaluation in candidate gene studies (15).

Furthermore, GWAS have so far identified genes in 15 chromosomal regions for AAA: *DAB2IP*, *LDLR*, *PSRC1-CELSR2-SORT1*, *CDKN2BAS1/ANRIL*, *IL6R*, *SMYD2*, *LINC00540*, *PCIF1-ZNF335-MMP9*, *ERG*, *AC012065.7/LDAH*, *MEPE*, *CDKN1A*, *RP11-136O12.2/TRIB1*, *LIPA*, *ZNF259/APOA5*, *ADAMTS8*, *CRISPLD2*, *CTAGE1*, *APOE*, *PCSK9*, *LPA*, *CHRNA3* and *ABHD16B* (10, 16-21). We thus explored the potential role of these AAA-risk loci with aortic diameter. Only one of these risk loci, namely *CDKN2BAS1/ANRIL* was associated with AAD in our combined meta-analysis.

ERG gene was found to be associated at nominal significance. The lack of genetic overlap between both traits may be determined by the limited power of this study.

Another explanation is that the disparities observed might indicate to what extent aging and cellular senescence are important to form aneurysms. Genes like *IL6R*, *MMP9*, *MMP13* and *CDNK2* are intimately related to cellular senescence; hence cellular

senescence-related pathways may have a great impact on the diameter of the abdominal aorta and its enlargement. *CDKN2BAS1/ANRIL*, located in the 9p21 chromosomal region, has been reported in numerous studies as a genetic risk locus for CAD, intracranial aneurysms, and diverse cardiometabolic disorders (32).

From the gene-based meta-analysis of exome array data we identified an association between *PCSK5* and AAD. *PCSK5* encodes a member of the subtilisin-like proprotein convertase family, which is involved in the trafficking of peptide precursors through regulated or constitutive branches of the secretory pathway (33). This is also an important finding given that conditional inactivation of endothelial *PCSK5* has shown decreased collagen deposition in the heart and in the vasculature in aged mice, and may be relevant to aortic dilation biology (34). *PCSK5* is thought to process prorenin, pro-membrane type-1 matrix metalloproteinase as well as lipoprotein metabolism-related pathways (35, 36). Furthermore, genetic variations at *PCSK5* locus have been associated with HDL-C levels possibly through the inactivation of endothelial lipase activity and atherosclerotic cardiovascular disease risk (36). *PCSK5* is also an important genetic predictor of tall stature as regulates the maturation of GDF15 (growth differentiation factor 15), a member of the TGF- β family, involved in body growth (37, 38). Although evidence is scarce, the role of this gene on the pathology of aortic diameter and aortic enlargement might be through collagen regulation and inflammatory pathways modulated by cholesterol metabolism and/or via activation of the renin-angiotensin system (39). In light of our findings, further research may be warranted.

Through the implementation of Mendelian randomization methods, we examined and determined if AAA-related risk factors may be causally associated with the variation of infrarenal aortic diameter observed in the studied population. MR uses genetic variants as proxies for the risk factor and the outcome of interest and can offer

an opportunity to shed light on the causality of risk factors-outcome associations (40). Unlike the associations of a risk factor with aortic enlargement reported from observational data, genetic associations are not influenced by reverse causation because the genotype is unmodified by the development of the disease. Moreover, the randomized assortment of parental alleles at conception tends to balance confounding factors among groups of differing genotypes (41).

In this study we used multiple independent SNPs as instrumental variables, selected from studies which have reported a robust association with each risk factor evaluated. We found evidence that genetic variation in height, pulse pressure and triglycerides is associated with variation in AAD, consistent with causal associations. Height, among the body size measurements, has shown the strongest association with aortic size. Evidence has demonstrated that height-based relative aortic measure predicts the risk of rupture, dissection, and death in patients with AAA (42). The association between height and AAA development and increasing risk of rupture might be explained by the presence of longer arteries in the AAA population (43). Nevertheless, the biological link between height and aortic enlargement remains unexplained.

Increased pulse pressure is associated with increased characteristic impedance (Z_c) of the aorta and increased load on the heart, contributing to the risk of ischemia (44), diastolic dysfunction (45) and adverse clinical events (46, 47). A high pulse pressure, markedly after mid-life when Z_c increases rapidly, may have an impact on the aortic diameter (48). Evidence has shown that higher pulse pressure in older people is associated with smaller aortic lumen area and greater aortic wall stiffness and thickness (49). A Small aortic diameter related with a higher pulse pressure suggests a mismatch in hemodynamic load accommodation by the heart and aorta in aged population. In contrast, a causal association between AAA and pulse pressure has not been established.

Pleiotropic effects are a major challenge in the implementation of Mendelian randomization (50). Instrumental variables that affect the outcome via pathways not including the exposure could distort or bias MR results. To address this, we performed sensitivity analyses including MR-Egger. Our MR-Egger result suggests a potential causal effect of triglycerides on AAD. Prospective studies have shown positive relationships between triglycerides and AAA (51-53). Moreover, triglycerides is strongly related to risk of ruptured AAA (54). In line with our findings, a large meta-analysis MR study have reported significant associations between triglycerides and abdominal aortic aneurysm (55).

In contrast, we found that there was not significant evidence for other genetically determined lipid fractions such as HDL-C and LDL-C having a causal effect on AAD. One explanation is that the genetic variants for LDL-C and HDL-C may explain a small proportion of the total variance in these lipid traits and this could affect their association with aortic diameter. Another explanation is that both lipids are indeed not causally related to AAD.

Our findings support the clinical importance of the management of blood pressure/pulse pressure and triglycerides for the prevention of AAA in high risk patients. Therefore, targeting risk factors related with aortic expansion at early stages could have important implications for the implementation of public health interventions aiming to reduce the prevalence of these risk factors and the morbidity and mortality caused by AAA.

Strengths and limitations

A key attribute of this study is the combination of a large discovery sample with standardized AAD measurement and dense 1000 Genomes imputation, which is the most common reference panel used in GWAS and offers excellent imputation for

common variants (56). Differences in the methods employed to measure AAD (ultrasound, MRI, CT-scan) may have introduced site-based effects into the study conferring error or bias in the measurements, which ultimately may have contributed to a lack of associated variants observed. We made use of log-transformed AAD to standardize the phenotype and minimize the impact of the variability present among the cohorts. We acknowledge several limitations in our work. The sample size for this GWAS has been the main limitation that hampered identifying further loci. However, we have searched extensively to include all studies with relevant data. Sexual dimorphism is relevant as it has been observed in the development of AAA (57). However, we did not perform sex-specific analyses given our limited sample size. In the context of gene-based analysis of exome array data, simulation studies have shown that in certain scenarios SKAT-O (58, 59) outperforms SKAT, as it combines both SKAT and burden tests, improving the power of the test. Therefore, we might have had a better statistical power if we had used SKAT-O. Our study population was of European ancestry. Generalizing the results to other ethnic groups should be done with caution.

Conclusions

In summary, we identified one replicated locus and one suggestive locus associated with the diameter of infrarenal aortic aorta. In addition, we provided evidence that the main genetic determinants of pulse pressure and height also causally influence the diameter of the abdominal aorta. In contrast, we found that other genetically determined risk factors for vascular-related diseases had no effect on AAD. Our findings point to new biology as well as highlighting gene regions in mechanisms that have previously been implicated in the genetics of other vascular outcomes. Larger sample sizes together with functional studies, investigating the translational potential of

these observations, are critical to characterize the molecular mechanisms regulated by the genes described in this study.

Materials and Methods

Participating studies

The study was done primarily in the framework of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, an international collaborative effort to facilitate GWAS meta-analysis and replication opportunities among multiple large cohorts (60). The discovery panel included European American participants from the Cardiovascular Health Study_European (CHS) (GWAS, n= 2,699; exome array, n=3,294), Cooperative Health Research in the Region Augsburg (KORA) (GWAS, n = 354; exome array, n=337), Framingham Heart Study_European (FHS) (GWAS and exome array, n = 3,262), Study of Health in Pomerania (SHIP-2 and SHIP-T) (GWAS, n = 1,010 [SHIP-2] and 827 [SHIP-Trend]; exome array, n= 2,848), The Multi-Ethnic Study of Atherosclerosis_European (MESA) (GWAS, n = 750; exome array, n=740), and the Rotterdam Study (RS) (GWAS, n = 3,913; exome array, n= 327) and BIOIMAGE (exome array, n=3,672). As a replication study, we used the Partners Biobank cohort (PBIO1) cohort (GWAS, n = 727). Details of the cohorts included are provided in **supplementary information (supplementary Table S1a, S1b and Table S2)**.

Abdominal aortic phenotypes

Maximum aortic diameter was defined as the largest measurement of anterior-posterior diameter of the infrarenal aorta measured by MRI, ultrasound or CT-scan using previously described reading protocols. Due to positive skewness, we used natural log-transformed AAD measurements. A description of the method employed in AAD measurement by each study is provided in methods in the **supplementary information**.

Genotyping and imputation

The studies employed SNP arrays available from Illumina or Affymetrix. Using available imputation techniques, each cohort imputed approximately >37 million variants from 1000 Genomes reference panel (phase 1 version 3) and applied strict quality control checks. Further information on the genotyping and imputation methods is detailed in **supplementary Table S3**.

Exonic and non-exonic variants were genotyped using the Illumina Infinium HumanExome BeadChip kit. The array covers > 240,000 markers, mostly coding variants discovered through exome sequencing in approximately 12,000 individuals and observed at least 3 times across at least 2 existing sequence datasets, and includes nonsynonymous, splicing, stop-altering variants, most of which are rare (http://genome.sph.umich.edu/wiki/Exome_Chip_Design). In order to ensure the accurate identification of variants and to minimize population stratification, exome array data quality control was performed based on Best Practices and Joint Calling of the HumanExome BeadChip: The CHARGE Consortium (61). Further details on methods employed by each study are outlined in **supplementary information**.

Statistical analyses within studies

Each study implemented GWAS and exome array data analyses based on a predefined analysis plan. We conducted linear regression models to evaluate the association of log-transformed AAD with genetic variations. For each variant, each study fitted additive genetic models regressing trait on genotype dosage (0–2 copies of the variant allele). In the primary model, each regression was adjusted by sex, age and principal components. Further adjustments including study site and/or familial structure were performed if necessary. We determined the association of each SNP with natural logarithm transformed AAD as the regression slope, its standard error and its

corresponding p-value. Furthermore, we examined 23 SNPs previously identified for AAA in GWAS and sought replication in our study (10, 16-18, 21, 62).

To conduct study-specific analyses on exome array data, all the studies used the prepScores function, implemented in the R package “SeqMeta” (63). Briefly, the prepScores function calculates scores and MAF for each variant interrogated within a gene. Log-transformed AAD was regressed against sex, gender and principal component analysis. Subsequently, the calculated prepScores by each cohort were combined in a single variant meta-analysis and gene-based meta-analysis.

Genome wide association study quality control and meta-analysis

Each cohort conducted a GWAS on AAD in adult subjects with genetic information available. Subsequently, GWAS summary statistics were uploaded to a central repository for QC and meta-analysis. We conducted data quality control at study file level of GWAS outputs using EasyQC (64) to identify file naming errors, erroneous SNP genotype data and false association caused by incorrect analysis models. We filtered out variants with a poor imputation quality (SNPTEST INFO value or MACH RSQR <0.4, Probabel <0.3) prior quality control. We further calculated genomic inflation for each study to determine population stratification or any other inconsistencies that might have inflated the test statistics. After QC, we meta-analyzed a range of 8.8-11.1 million of variants per study. The meta-analysis of linear regression estimates and standard errors using an inverse-variance weighting approach was conducted using METAL (65). We reported SNPs that were present in at least five studies and with an average MAF of at least 1%. Variants with a meta-analyzed p-value $\leq 5 \times 10^{-8}$ were considered significant.

A gene-set analysis of GWAS data was done using MAGMA v1.06 (66). Gene-based results were used to perform a tissue enrichment analysis implemented in GTEX. Additional information is provided in **supplementary information**.

Meta-analysis of rare exonic variants from exome array

Study-specific summary statistics, such as estimated regression coefficient for each variant and its standard error (prepScores) were meta-analyzed on single variant level, to perform score tests for single SNP associations, and in a gene-based test [sequence kernel association test (SKAT)] using seqMeta (63). SKAT directly performs multiple regressions models, neither directionality nor magnitudes of the associations are assumed a priori but are instead estimated from the data (67). Hence, SKAT is robust to the magnitude and direction of genetic effects as well as to the presence of neutral variants (67). Single variant results were filtered for a pooled MAF > 0.005 and those included in at least 50% of the cohorts were reported. Furthermore, variants with MAF ≤ 5% were included in the gene-level test. Additional arguments implemented in SKAT meta-analysis allowed us to specify the method of p-values calculation. We used the default method “saddlepoint”, which appears to have higher relative accuracy (63, 68). We defined a statistical significance threshold of single variant and gene-based exome array meta-analysis based on Bonferroni correction for multiple testing, ~55,434 variants (p-value < 9×10^{-7}) and ~16,378 genes (p-value < 3×10^{-6}), respectively. Genetic variants in exome array were annotated using SNPInfo file 12 version 1.0.

SNP Heritability and genetic correlation

To characterize the extent to which SNPs determine AAD, and shared genetic etiology with other traits (AAA, coronary artery disease and stroke), we applied linkage disequilibrium score regression (LDSC) (69). We used the default European LD score file based on the European 1KG reference panel. The analyses were conducted using

LDSC (LD SCore) v1.0.1. (69, 70). Further information is detailed in **supplementary information**.

Identification of expression quantitative trait loci (eQTL)

Furthermore, we examined the effect of associated genetic variants on the expression of genes in *cis* and *trans*. To characterize their effects, we first sought SNP associated with gene expression from the Genotype-Tissue Expression Project (GTEx portal, Analysis Release V7) a platform with available expression data on potential target organs (heart tissue, kidney tissue, brain tissue, aortic endothelial cells and blood vessels) as well as blood cell types (CD4+ macrophages, monocytes) (71). The gene expression values are shown in TPM (transcripts per million), calculated from a gene model with isoforms collapsed to a single gene. Box plots are shown as median and 25th and 75th percentiles, outliers are displayed as dots if they are above or below 1.5 times the interquartile range (71). In addition, the platform also allows the assessment of isoform expression generated using RSEM, software package for estimating gene and isoform expression levels from RNA-Seq data.

Genetic risk score and Mendelian randomization analysis

In order to determine the additive association of AAA-related SNPs on AAD, we combined the effect size of each AAA-SNP reported up to date in a weighted genetic risk score (GRS), and tested its association with AAD in the Rotterdam Study Cohort (n=3,913).

We implemented a two-sample Mendelian randomization analysis to evaluate causal effects of a number of risk factors on AAD. Risk factors were chosen based on previous literature reporting them to be associated with AAA. We identified genetic instruments for systolic blood pressure (SBP) (72, 73), diastolic blood pressure (DBP) (72, 73), pulse pressure (PP) (72, 73), smoking (74, 75), low-density lipoprotein (LDL),

high-density lipoprotein (HDL) and triglycerides (TG) (76, 77), height (78), and body mass index (BMI) (79, 80) using the most up-to-date GWAS on these traits. We used the inverse variance weighted (IVW) method to combine the effect of multiple instruments. We further used two sensitivity analyses, the weighted median and MR-Egger, to investigate potential effect of pleiotropic variants on the estimates. For lipid traits, we used a multivariable MR method (81). In this approach, a single regression model with outcome variable (β for AAD) was fitted for each of the predictor variables (β for LDL, β for HDL, and β for TG). The model was implemented as a multilinear regression of SNP association estimates weighted by the inverse variances of the estimated associations of SNPs with the outcome.

All MR methods for multiple genetic instruments were conducted using “MendelianRandomization”, a statistical package running under R (<https://cran.r-project.org/web/packages/MendelianRandomization/index.html>) (82). We used MR-PRESSO (Mendelian randomization pleiotropy residual sum and outlier) to identify horizontal pleiotropic outliers in multi-instrument summary-level MR testing (<https://github.com/rondolab/MR-PRESSO>) (83). Further details are outlined in **Supplementary information.**

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Conflict of Interests

The authors declare no conflict of interest.

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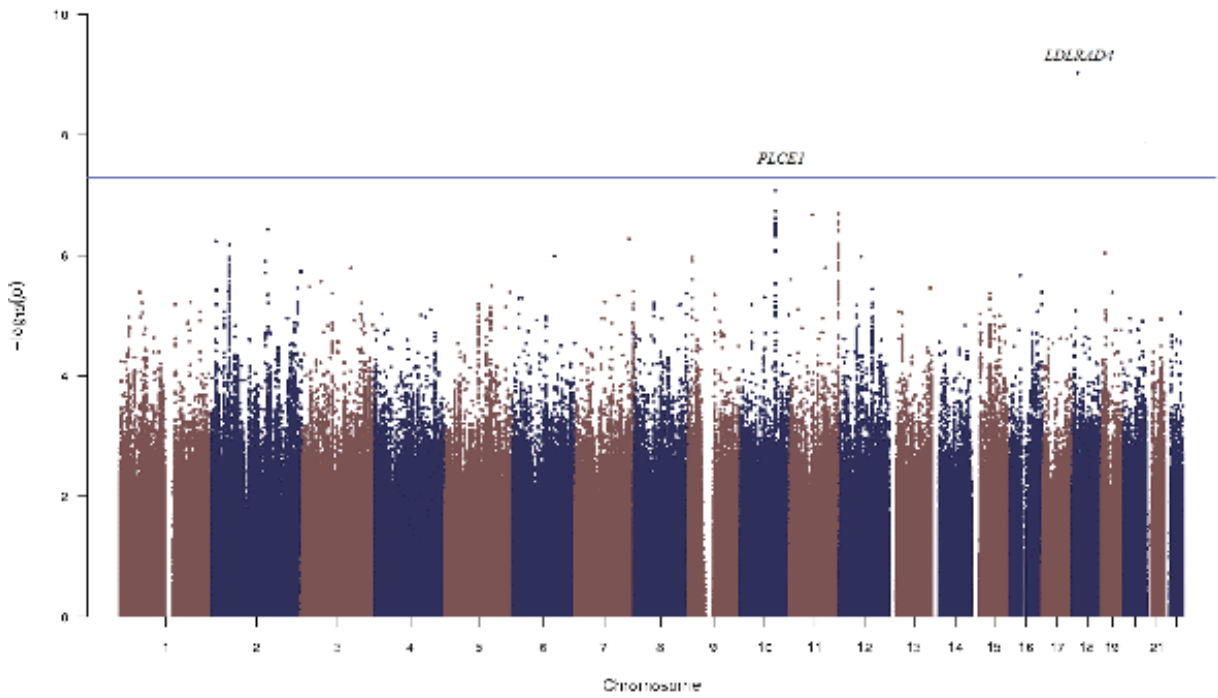


Figure 1. Manhattan plot of meta-analysis of genome-wide association studies on abdominal aortic diameter. Manhattan plot showing the $-\log_{10}$ -transformed p-value of SNPs in the GWAS of abdominal aortic diameter. The blue line indicates the GWAS-significance level (p-value $< 5 \times 10^{-8}$).

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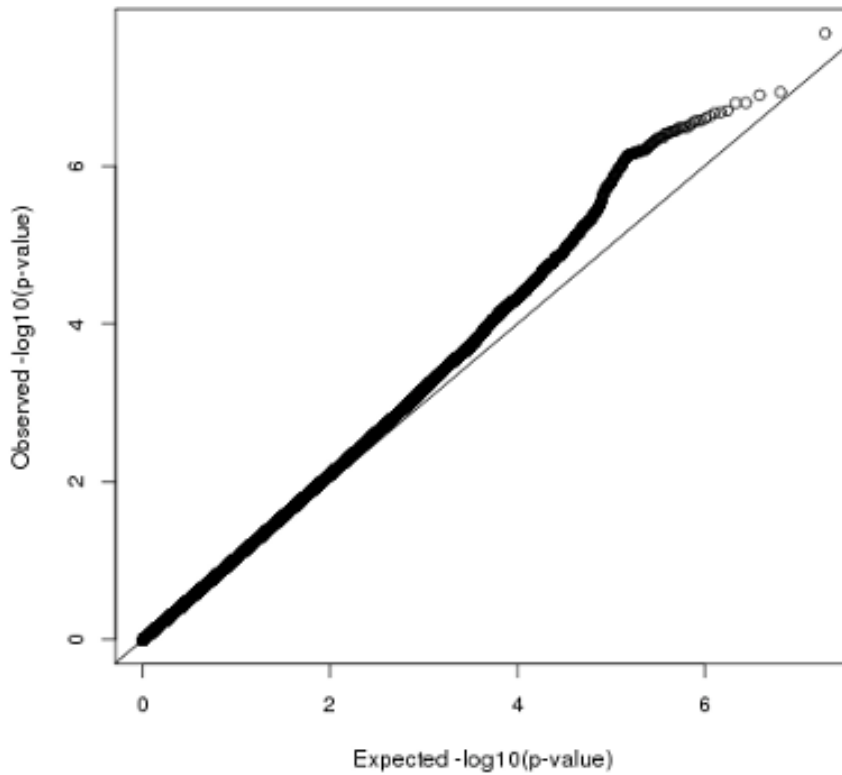


Figure 2. Quantile-quantile plot of genome-wide association studies on abdominal aortic diameter. Vertical and horizontal lines represent expected p-values under a null distribution and observed p-values, respectively.

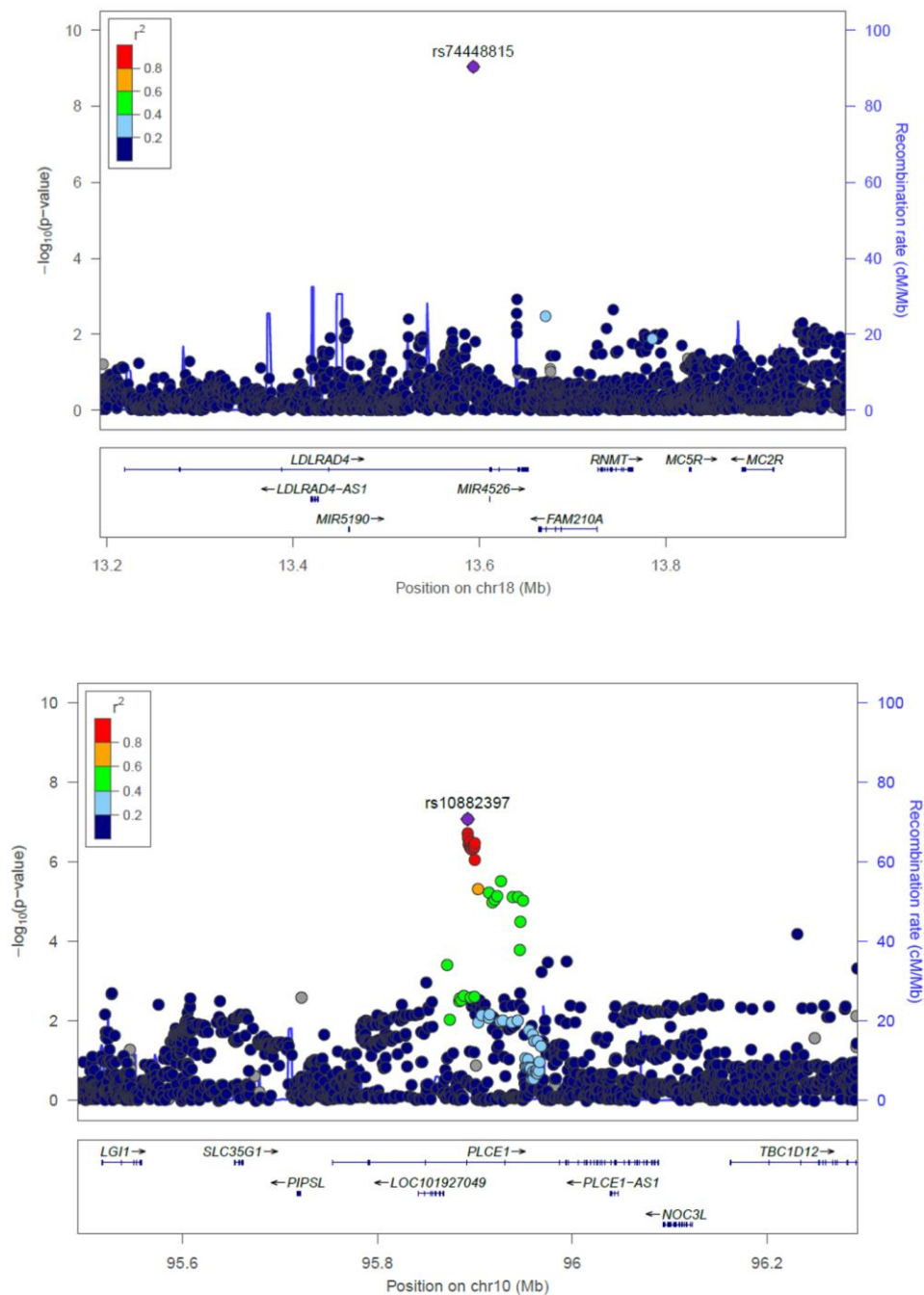


Figure 3. Regional plots showing the association of *LDLRAD4* and *PLCE1* genes with abdominal aortic diameter. P-values of genotyped SNPs (circle) and imputed SNPs (square) are plotted (as $-\log_{10}P$ value) against their physical location on chromosome 18p11.21 (a) and 10q23.33 (b). SNP's color indicates LD with rs74448815 (a), rs10882397 (b) according to a scale from $r^2 = 0$ to 1 based on pair-wise r^2 values from 1000 Genomes.

Table 1. Associated and suggestive associated loci with abdominal aortic diameter in GWAS

Locus	Chr	SNP	maf	A1/A2	β	p-value combined	p-value in discovery cohort	p-value in replication cohort
<i>LDLRAD4</i>	18	rs74448815	0.04	A/C	-0.02	9.15×10^{-10}	2.1×10^{-8}	8.19×10^{-4}
<i>PLCE1</i>	10	rs10882397	0.46	A/C	0.008	8.37×10^{-8}	2.13×10^{-7}	0.14
<i>ADAMTS15</i> - <i>C11orf44</i>	11	rs1689231	0.38	C/G	-0.008	3.81×10^{-7}	2.7×10^{-7}	0.95

A1: Coded allele; A2: non-coded allele; Chr: Chromosome, maf: minor allele frequency, s.e: standard error

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Table 2. Association of the previously identified risk loci for AAA with abdominal aortic diameter

SNP	Nearest gene	A1/A2	β^*	p-value**
GWAS				
rs602633	<i>PSRC1-CELSR2-SORT1</i>	T/G	0.002	0.32
rs4129267	<i>IL6R</i>	T/C	-0.001	0.47
rs10757274	<i>CDKN2BAS1/ANRIL</i>	A/G	-0.006	1.71×10^{-4}
rs10985349	<i>DAB2IP</i>	T/C	-0.001	0.58
rs6511720	<i>LDLR</i>	T/G	0.001	0.74
rs1795061	<i>SMYD2</i>	T/C	0.002	0.35
rs9316871	<i>LINC00540</i>	A/G	0.002	0.35
rs3827066	<i>PCIF1-ZNF335-MMP9</i>	T/C	0.002	0.44
rs2836411	<i>ERG</i>	T/C	0.003	0.036
rs7255	<i>AC012065.7/LDAH</i>	C/T	0.003	0.08
rs10023907	<i>MEPE</i>	T/C	0.003	0.07
rs3176336	<i>CDKN1A</i>	A/T	-0.002	0.21
rs10808546	<i>RP11-136O12.2/TRIB1</i>	T/C	-0.001	0.38
rs1412445	<i>LIPA</i>	T/C	-0.001	0.46
rs964184	<i>ZNF259/APOA5</i>	C/G	0.001	0.52
rs4936098	<i>ADAMTS8</i>	A/G	-0.003	0.03
rs35254673	<i>CRISPLD2</i>	A/G	0.002	0.29
rs4401144	<i>CTAGE1</i>	T/C	0.003	0.07
rs429358	<i>APOE</i>	T/C	0.001	0.57
rs11591147	<i>PCSK9</i>	T/G	0.004	0.72
rs118039278	<i>LPA</i>	A/G	0.001	0.69
rs55958997	<i>CHRNA3</i>	A/C	-0.001	0.54
rs73149487	<i>ABHD16B</i>	T/G	-0.0008	0.86
Candidate-gene studies				
rs599839	<i>SORT1</i>	A/G	-0.001	0.46
rs7529229	<i>IL6R</i>	T/C	0.001	0.48
rs6743376	<i>IL1RN</i>	A/C	0.0001	0.93
rs1542176		T/C	-0.0006	0.68
rs10455872	<i>LPA</i>	A/G	-0.002	0.52
rs3798220		T/C	0.007	0.26
rs5186	<i>AGTR1</i>	A/C	-0.002	0.17
rs1036095	<i>TGFBR2</i>	C/G	0.001	0.53
rs764522		C/G	-0.003	0.08

A1: Coded allele; A2: non-coded allele; Chr: Chromosome, p-value threshold= 0.003

* Beta coefficients from combined AAD meta-analysis

** p-value from combined AAD meta-analysis

Table 3. Association of the identified AAD-SNPs with vascular traits

SNP	Nearest gene	p-value	Trait
rs74448815	<i>LDLRAD4</i>	0.95	AAA
		0.005	CAD
rs932764	<i>PLCE1</i>	6.88×10^{-17}	SBP
		6.28×10^{-10}	DBP
rs2797983		1.34×10^{-4}	AAA

CAD: coronary Artery Disease; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AAA: abdominal aortic aneurysm

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Table 4. Mendelian randomization results for each risk factor

Systolic blood pressure			
Method	Estimate	p-value	p-value heterogeneity (IVW)
IVW	-0.001	0.2	0.04
MR-Egger	0.001	0.8	-
MR-Egger (intercept)	0	0.6	-
Weighted median	0.0001	0.9	-
Diastolic blood pressure			
IVW	-0.001	0.6	0.2
MR-Egger	-0.002	0.5	-
MR-Egger (intercept)	0	0.6	-
Weighted median	0.001	0.8	-
Pulse pressure			
IVW	-0.003	0.02	0.02
MR-Egger	-0.009	0.04	-
MR-Egger (intercept)	0	0.1	-
Weighted median	-0.003	0.06	-
Smoking			
IVW	0.02	0.3	0.03
MR-Egger	0.01	0.9	-
MR-Egger (intercept)	0	0.9	-
Weighted median	-0.006	0.8	-
LDL			
IVW	-0.005	0.2	0.04
MR-Egger	-0.004	0.5	-
MR-Egger (intercept)	0.0001	0.8	-
Weighted median	-0.006	0.3	-
HDL			
IVW	-0.002	0.9	0.002
MR-Egger	-0.02	0.8	-
MR-Egger (intercept)	0	0.8	-
Weighted median	0.009	0.7	-
Triglycerides			
IVW	-0.02	0.2	0.2
MR-Egger	-0.16	0.008	-
MR-Egger (intercept)	0.003	0.01	-
Weighted median	-0.03	0.1	-
Height			
IVW	0.03	0.0001	0.05
MR-Egger	0.07	0.0001	-
MR-Egger (intercept)	-0.001	0.008	-
Weighted	0.03	0.0001	-

median			
BMI			
IVW	0.01	0.0001	0.06
MR-Egger	0.004	0.3	-
MR-Egger (intercept)	0.001	0.001	-
Weighted median	0.004	0.26	-

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Abbreviations

AAA	Abdominal aortic aneurysm
AAD	Abdominal aortic diameter
ABHD16B	Abhydrolase Domain Containing 16B
ADAMTS15	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 15
ACE	Angiotensin I Converting Enzyme
AGTR1	Angiotensin II Receptor Type 1
APO	Apolipoprotein
BMI	Body mass index
CAD	Coronary Artery Disease
CDKN1A	Cyclin Dependent Kinase Inhibitor 1A
CELSR2	Cadherin EGF LAG Seven-Pass G-Type Receptor 2
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CHRNA3	Cholinergic Receptor Nicotinic Alpha 3 Subunit
CHS	Cardiovascular Health Study
CRISPLD2	Cysteine Rich Secretory Protein LCCL Domain Containing 2
CT	Computed tomography
CTAGE1	Cutaneous T Cell Lymphoma-Associated Antigen 1
DAB2IP	DAB2 Interacting Protein
DBP	Diastolic blood pressure
ERG	ETS Transcription Factor ERG
eQTL	Expression quantitative trait loci
FHS	Framingham Heart Study
GDF15	Growth differentiation factor 15
GRS	Genetic risk score
GTE _x	Genotype-Tissue Expression Project

GWAS	Genome wide association study
HDL	High-density lipoprotein
IL6R	Interleukin 6 Receptor
IVW	Inverse-variance weighting
KORA	Cooperative Health Research in the Region Augsburg
LD	Linkage disequilibrium
LDAH	Lipid Droplet Associated Hydrolase
LDL	Low-density lipoprotein
LDLRAD4	Low Density Lipoprotein Receptor Class A Domain Containing 4
LDSC	Linkage disequilibrium score regression
LIPA	Lipase A, Lysosomal Acid Type
LPA	Lipoprotein(A)
LRP5	LDL Receptor Related Protein 5
MAF	Minor allele frequencies
MEPE	Matrix Extracellular Phosphoglycoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
MMP	Matrix Metalloproteinase
MR	Mendelian Randomization
MRI	Magnetic resonance imaging
MTHFD1	Methylenetetrahydrofolate Dehydrogenase, Cyclohydrolase And Formyltetrahydrofolate Synthetase 1
MTRR	5-Methyltetrahydrofolate-Homocysteine Methyltransferase Reductase
PBIO1	Partners Biobank cohort 1
PCSK5	Proprotein Convertase Subtilisin/Kexin Type 5
PCIF1	Phosphorylated CTD Interacting Factor 1
PLCE1	Phospholipase C Epsilon 1
PP	Pulse pressure

PSRC1	Proline And Serine Rich Coiled-Coil 1
RS	Rotterdam Study
SBP	Systolic blood pressure
SHIP	Study of Health in Pomerania
SLC22A20	Solute Carrier Family 22 Member 20
SIM	SIM BHLH Transcription Factor
SMAD	SMAD Family Member
SMYD2	SET And MYND Domain Containing 2
SNP	Single nucleotide polymorphism
SORT1	Sortilin 1
TG	Triglycerides
TGF	Transforming growth factor
TPM	transcripts per million
TRIB1	Tribbles Pseudokinase 1
WES	whole exome sequencing
ZFYVE9	Zinc Finger FYVE-Type Containing 9